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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,639	THIRY ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7,9-16,18-23,25-27,30-36 and 44-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,7,9-16,18-23,25-27,30-36 and 44-60* is/are rejected.

7)☒ Claim(s) *7,9-16,20-23,25-27,30-36 and 44-54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/24/08 has been entered.

Claims 1, 4, 6-7, 9-16, 18-23, 25-27,30-36 and 44-60 are pending and under examination. Claims 46-58 are new. Claims 2-3, 5, 8, 17, 24, 28-29, 37-43 have been cancelled.

Information Disclosure Statement

The information disclosure statement filed 10/6/08 has been considered. An initialed copy is enclosed.

Objections/Rejections withdrawn

The objection to claims 25, 27, 30, 31 and 34 for being improper dependent form is withdrawn upon further consideration.

The objections to claims 4, 6, 7-36 and 43-45 are withdrawn upon further consideration.

The rejection of claims 34-36 and 44 under 35 U.S.C. 112, first paragraph (scope of enablement) is withdrawn in view of the amendment to the claims and in favor of a new rejection set forth below.

The rejection of claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (lack of complete deposit information) is withdrawn in view of the cancellation of the claims.

The rejection of claims 8 and 43 under 35 U.S.C. 101 is withdrawn in view of the cancellation of the claims.

The rejection of claims 8 and 43 under 35 U.S.C. 102(b) as being anticipated by New England Biolabs Catalog, 1996/1997 p. 111 – Random primers is withdrawn in view of the cancellation of the claims.

New Claim Objections/Rejections

Claim Objections

Claim 45 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 22. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Both claims are drawn to a vaccine comprising the recombinant Yersinia ruckeri of claim 16.

Claims 7, 9-16, 20-23, 25-27, 30-36 and 44-54 are objected for broadening the scope of claim 1. Claim 1 is drawn to isolated p45 protein or recombinant polypeptide comprising the

amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution.

Claim 7 and dependent claims are drawn to the nucleic acid encoding the p45 protein or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution wherein the nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3. Claim 7 broadens claim 1 because, for example, when each amino acid residue of the proteins of claim 1 are completely conservatively substituted, the scope of the nucleic acid of claim 7 covers substitutions in all of the residues of the completely conservatively substituted proteins of claim 1 to yield SEQ ID NO: 1 which encodes SEQ ID NO: 2 or SEQ ID NO: 3 which encodes SEQ ID NO: 4.

Claim 46 and dependent claims are drawn to the isolated p45 protein or recombinant polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. Claim 46 broadens claim 1 because, for example, when each amino acid residue of the proteins of claim 1 are completely conservatively substituted, the scope of claim 46 covers substitutions in residues of the completely conservatively substituted proteins of claim 1 to yield SEQ ID NO: 2 or SEQ ID NO: 4. Thus claim 46 broadens the scope of claim 1. Claim 51 and dependent claims are drawn to the p45 protein or recombinant polypeptide of claim 1 wherein the p45 protein has at least 95% identity with the amino acid sequence of SEQ ID NO: 2 and/or SEQ ID NO: 4. Claim 51 broadens claim 1 because claim 51 further comprises non-conservative substitutions, insertion, and/or deletions to the at least one conservatively amino acid substituted sequences of claim 1. Thus, claim 51 broadens the scope of claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-23, 25-27, 30-36, 44-45, 54 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims (18-23, 25-27, 30-36, 44-45 and 59-60) are drawn to a vaccine that comprises an isolated p45 protein or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution; a vaccine that comprises the nucleic acid that encodes said p45 protein or recombinant polypeptide; a vaccine comprising host cell that comprises a expression vector that comprises the nucleic acid sequence that encodes p45 protein or recombinant polypeptide and methods of protecting a fish comprising administering any of the above vaccines.

Claim 54 is drawn to a vaccine that comprises the expression vector comprising a nucleic acid that encodes an isolated p45 protein or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution wherein the p45 protein has at least 95% identity with the amino acid sequence of SEQ ID NO: 2 and/or SEQ ID NO: 4.

Claim 58 is drawn to a vaccine comprising an expression vector that comprises a nucleic acid encoding an isolated p45 protein or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 wherein the p45 protein has at least 95% identity with the amino acid sequence of SEQ ID NO: 2 and/or SEQ ID NO: 4.

The specification teaches that SEQ ID NO: 2 is the full length p45 protein and SEQ ID NO: 4 is the p45 protein without the signal sequence and from the teachings in the specification there is no amino acid variability in the amino acid sequence of SEQ ID NO: 4 and the portion of SEQ ID NO: 2 which does not have the signal sequence.

As to a *P. salmonis* 45 kDa protein (p45) or recombinant polypeptide comprising SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitutions, this encompasses a genus of variants of said proteins comprising a range of different conservative amino acid substitutions i.e. conservative substitutions at 1 or 2 or 3 residues up to all residues of the full sequence being conservatively substituted. The conservative substitution(s) can occur anywhere in the proteins. Claim 54 expands said genus because said proteins of said genus of conservatively substituted variants have at least 95% identity with the amino acid sequence of SEQ ID NO: 2 and/or SEQ ID NO: 4. This encompasses non-conservative amino acids substitutions, deletions and insertions. Claim 58 is drawn to a genus of variants of SEQ ID NO: 2

or SEQ ID NO: 4 comprising changes in up to 5% of the respective sequences. This covers substitutions, insertions and deletions in any 5% or less of the sequences.

The specification does not describe the immunoepitopes of p45 protein (with or without signal peptide). The specification does not teach the protective immunoepitope(s) of a p45 protein or SEQID NO: 2 or SEQ ID NO: 4 so that one of skill in the art can envision which regions of the amino acid can be conservatively substituted and still retain immunogenicity and protectiveness. Further, the specification does not teach which 5% or 4% or 3% or 2% or 1% of the amino acid sequence of the members of said genus of conservatively substituted variants can be changed and still retain the ability to protect against infection. The specification does not teach which 5% or 4% or 3% or 2% or 1% of SEQ ID NO: 2 or SEQ ID NO: 4 can be changed and still retain the ability to protect against infection. The claims are drawn to a large number of variants having different possibilities of changes to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The specification does not teach an example of any variant of the instant proteins including those that comprise at least one conservative amino acid substitution that still protects from infection. The specification does not teach that the immunoepitopes are still retained when the proteins are conservatively substituted. The specification does not for example teach that protectiveness is retained when all the amino acid positions of the protein are conservatively substituted.

The dictionary definition of vaccine is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity)." (The Dictionary of Immunology, Herbert et al eds,

Academic Press, 1995). Antibody epitopes are characterized by the art as either continuous or discontinuous (see pages 23-25, 27-33, Harlow et al , Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory Press Inc., 1988). T cell epitopes are continuous peptide fragments of a polypeptide or antigen that have been processed by an accessory cell. The art recognizes that defining epitopes is not easy and there is a confusing divergence between the textbook definition of epitope and the definition that is in use in published descriptions of experimental investigations and that epitopes must be empirically determined (Greenspan et al, Nature Biotechnology 17:936-937, 1999). The specification clearly lacks description of any particular antibody epitope (i.e. antigenic determinant), either continuous or discontinuous that is within SEQ ID NO: 2 or SEQ ID NO: 4. These particular characteristics of the B or T cell epitope is required by the definition of "vaccine". Applicants clearly did not provide written description of any particular antibody-binding or T-cell binding epitope contained in the instant proteins and as such it is not clear which residue(s) can be altered and still function as a vaccine as contemplated by the specification and claims. The fact that one could screen for epitopes that are protective is not the standard for written description. The specification lacks written description of the instant variants that are protective when administered. For example, Colman et al. (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that a single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect in antibody binding. This underlies the importance of the description of the immunoepitopes that are protective and which conservative amino acid substitutions and where and how many changes can the immunoepitopes tolerate and still retain

the ability to protect from infection. Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

Even though one could screen for which changes in SEQ ID NO: 2 or SEQ ID NO: 4 will maintain protection from infection, the courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus or how to identify their common structural features. The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) and adequate written description requires more than a mere reference to a potential method for identifying candidate polypeptides. The purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). The disclosure of only two members of the genus to which the claims are drawn full length p45 protein (SEQ ID NO: 2) and p45 protein without the signal peptide (SEQ ID NO: 4) is insufficient to describe the large and variant genus of proteins the scope of which is set forth above. In such an unpredictable art, as set forth supra, adequate written description of a genus which embraces widely variant species cannot be achieved by

disclosing only one species within the genus. See *Noelle v Lederman*. 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (*Fed. Cir. 2004*) and *In re Alonso* (Fed. Cir. 2008-1079).

Since the specification does not describe the common structure i.e. the protective immunoprotective epitope(s) possessed by said genus, the skilled artisan would not be able to readily envision which changes could be made to SEQ ID NO: 2 or SEQ ID NO: 4 that still maintain protection against infection. Except for SEQ ID NO: 2 or SEQ ID NO: 4, the specification lacks written description for variants SEQ NO: 2 or variants of SEQ ID NO: 4 that can protect from infection (i.e. a vaccine) and Applicants as of the time of filing were not in possession of said variants.

Claims 1, 4, 6-7, 9-16, 18-23, 25-27, 30-36 and 44-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) an isolated *Piscirickettsia salmonis* 45 kDa protein comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acids encoding said proteins and expression vectors and host cells comprising nucleic acids encoding SEQ ID NO: 2 or SEQ ID NO: 4;

2) an immunogenic composition comprising SEQ ID NO: 2 or SEQ ID NO: 4 and an immunogenic composition comprising a recombinant *Yersinia ruckeri* comprising an expression vector comprising the nucleic acid that encodes SEQ ID NO: 2 or SEQ ID NO: 4

3) enabling for a method of delaying the occurrence of infection by *P. salmonis* and reducing mortality due to *P. salmonis* infection in salmonid fish comprising administering an immunogenic composition as set forth above;

does not reasonably provide enablement for:

an isolated *Piscirickettsia salmonis* 45 kDa protein comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution and nucleic acids encoding such host cells comprising said either of said nucleic acids; does not provide enablement for said proteins comprising at least one conservative amino acid substitution and have at least 95% identity with SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acids encoding such and host cells comprising either of said nucleic acids; does not provide enablement for vaccines and does not provide enablement for a method of protecting fish from salmonid rickettsial septicemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Independent claim 1 and dependent claims are drawn to an isolated *Piscirickettsia salmonis* 45 kDa protein comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution. The breadth of independent claim 1 encompasses variants of the instant sequences wherein one or several residues or all of the residues of SEQ ID NO: 2 or SEQ ID NO: 4 are conservatively substituted.

As to claims 1, 4, 6, 30-36 and 51-53, the disclosed use of the instant SEQ ID NO: 2 and SEQ ID NO: 4 comprising at least one conservative amino acid substitution and nucleic acids encoding such is for a vaccine to protect fish against *P. salmonis* infection (specification p. 3-4

under summary of the invention) or to make antibodies to be used in diagnostic kits or components in vaccines (p. 29 lines 22 to 29).

As to claims 55-58, the disclosed use of an isolated protein comprising SEQ ID NO: 2 or SEQ ID NO: 4 wherein the protein has 95% identity with the amino acid sequence of SEQ ID NO: 2 and/or SEQ ID NO: 4 and nucleic acids encoding such is for a vaccine to protect fish against *P. salmonis* infection (specification p. 3-4 under summary of the invention) or to make antibodies to be used in diagnostic kits or components in vaccines (p. 29 lines 22 to 29).

The specification teaches that the p45 protein is obtained from the bacterium *Piscirickettsia salmonis* (see background p. 1-3 of the specification). The specification discusses other antigens obtained from other infectious agents infecting fish such as the VP2 and VP3 protein of the infectious pancreatic necrosis (IPN) virus. The specification teaches that a composition comprising a bacterin of *Yersinia ruckeri* carrying the full length nucleic acid encoding p45 antigen (SEQ ID NO: 2 with signal peptide) and oily adjuvant (Montanide ISA711) is administered to Atlantic salmon (see example 4 lines 11-24, example 7 p. 79-86).The specification teaches that relative percent survival (RPS) in vaccinated fish was 100% when the control mortality was greater than or equal to 60% whereas at the end of the trial RPS for the vaccinated group was 43.4% and that the results indicate that SRS was effective in reducing mortality from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10).

As to the issue of SEQ ID NO; 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution, the specification however does not teach immunization with the *Y.*

ruckeri comprising a nucleic acid molecule encoding a SEQ ID NO: 2 or 4 comprising one or more conservative amino acid substitutions. The specification does not disclose the protective immunoepitopes of the p45 antigen full length (SEQ ID NO: 2) or without signal peptide (SEQ ID NO: 4). The specification does not correlate conservative acid substitutions in SEQ ID NO: 2 or SEQ ID NO: 4 with protection from salmonid rickettsial septicemia or reduction in mortality from challenge with *P. salmonis* or with production of antibodies specific for P. salmonis. The specification does not provide guidance as to whether the immunoprotective epitopes of SEQ ID NO: 2 or SEQ ID NO: 4 is maintained when the sequences comprise one or more conservative substitutions. For instance, conservative substitution of all positions of SEQ ID NO: 2 or SEQ ID NO: 4 results in a completely different protein sequence and the specification does not provide guidance as to whether this different protein can still protect against salmonid rickettsial septicemia (SRS) or reduction in mortality from challenge with *P. salmonis*. Similarly, the specification does not teach whether conservatively substituted variants of SEQ ID NO: 2 or SEQ ID NO 4 which have least 95% identity to SEQ ID NO: 2 or SEQ ID NO: 4 (see claim 51 and dependent claims) protects from infection. The scope comprises conservatively substituted variants of SEQ ID NO: 2 or SEQ ID NO: 4 which further comprises other non-conservative substitutions (i.e. SEQ ID NO: 2 or 4 comprising multiple mutations). As set forth above, the specification also does not provide for uses (vaccines or making antibodies) of variants of the p45 antigen (conservatively substituted and/or 95% identical to SEQ ID NO: 2 and/or SEQ ID NO: 4). Houghten et al (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) teaches the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One

could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, guidance and/or working example is needed correlating one or more conservative amino acid substitutions and other non-conservative amino acid changes (deletions or insertions) in SEQ ID NO: 2 or SEQ ID NO: 4 with protection from P. salmonis or for production of antibodies that detect P. salmonis.

As to vaccines being claimed (claims 18-23, 25-27, 30, 45, 49-50, 54 and 58-60) and methods of protecting a fish from SRS (claims 31-36 and 44): The dictionary definition of vaccine is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity) " (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995). As set forth above, the specification teaches that a composition comprising *Y. ruckeri* comprising nucleic acid encoding the full length p45 antigen with signal peptide and oily adjuvant was effective in reducing mortality and delaying infection from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10). Thus, the specification provides for delaying of infection and reducing mortality but does not protect from infection as set forth in the definition of a vaccine and also does not correlate delaying of *P. salmonis* infection and reducing mortality with protecting any fish from

salmonid rickettsial septicemia. Furthermore, as to broad protection of all fish, the specification does not correlate delay of *P. salmonis* infection and reduction in mortality seen in the salmonid fish with immunoprotective responses in other non-salmonid fish. The specification mentions that there is a link between *Piscirickettsia* -like bacteria and disease syndromes in non-salmonid fish (p. 1 lines 35-37) and that the instant p45 antigen can be used to protect against *Piscirickettsia* -like bacteria. However, the specification does not provide guidance as to whether these *Piscirickettsia* -like bacteria comprise the p45 antigen and whether the p45 antigen is cross protective for protecting non-salmonid fish from *Piscirickettsia* -like bacteria. It is unpredictable that p45 antigen protects non-salmonid fish from *Piscirickettsia* -like bacteria since is not known whether *Piscirickettsia* -like bacteria also comprises SEQ ID NO: 2 (p45 antigen). In view of the guidance in the specification, the specification is enabling for a method of delaying the occurrence of infection by *P. salmonis* and reducing mortality due to *P. salmonis* infection in salmonid fish comprising administering an immunogenic composition comprising SEQ ID NO: 2 or SEQ ID NO: 4 or an immunogenic composition comprising expression vector that comprises the nucleic acid encoding SEQ ID NO: 2 or SEQ ID NO: 4 or an immunogenic composition comprising *Y. ruckeri* comprising an expression vector that comprises the nucleic acid encoding SEQ ID NO: 2 or SEQ ID NO: 4. In addition, as to protecting fish from SRS and Infectious Pancreatic Necrosis (claims 34-36), as mentioned the specification provides for protecting salmonid and does not provide for all fish. Also, in protecting salmonids against infectious pancreatic necrosis (IPN) and SRS, the specification teaches that a composition comprising *Yersinia ruckeri* carrying the p45 antigen and particular antigens IPN antigens VP2 and VP3 are administered to Atlantic salmon and said composition is efficacious and provides

for a reduction in mortality (93.6% survival when control group is at 60% mortality and 30% survival when control group is at 94% survival) when said salmon is challenged with *P. salmonis*. See example 8 p. 86-89. The specification does not provide guidance as to other IPN antigens which in combination with the p45 antigen and administered to salmonid fish reduces mortality and delays occurrence of infection due to IPN virus. Claims 34-36 are broadly drawn to any antigen obtained from IPN virus. The art teaches that VP2 and VP3 viral capsid antigens of IPN virus reduced mortality after virus challenge (Leong et al US 5,165,925 Nov. 24, 1992, fig 14, column 15-column 16 under vaccine trial), however the specification does not provide guidance as other IPN antigens and/or their immunoepitopes that protects against IPN.

As to a vaccine comprising an isolated or recombinant nucleic acid encoding the isolated p45 protein or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution (claims 6 and 31 and dependent claims), the specification does not provide any guidance or working example as to immune responses generated by said nucleic acid molecules and whether the immune responses generated by the nucleic acid molecule is effective against *P. salmonis*. It is not clear that when the nucleic acid molecule(s) without the necessary expression sequences is administered to salmon fish, the nucleic acid molecule by itself will express protein which can be processed by the immunological machinery for induction of immune responses. Naked DNA for vaccine therapy is known in the art but the DNA encoding the protein is cloned into a plasmid and the plasmid DNA encoding the antigen is administered to a patient (usually intramuscularly) and the plasmid DNA is taken up by antigen presenting cells leading to the expression of the antigen via transcription of the DNA into mRNA (See Molling et al. J Mol. Med (1997) 75: 242-246, fig. 1).

It is unpredictable that the instant nucleic acid molecules without the appropriate transcription unit that directs antigen synthesis can be expressed as protein in a fish cell (Tighe et al. Immunology Today vol. 19, p. 89-97 see whole document especially fig. 3).

Further, certain bacterial DNA are known to contain CpG motifs which can elicit a non-specific immune response, the therapeutic application of oligonucleotides containing the CpG motifs have been limited to short oligonucleotide sequences comprising said motifs. The use of such short oligonucleotide sequences for inducing immune responses is dependent on many factors including the sequence context of the CpG dinucleotide, the length of the sequence, the species specificity of the oligonucleotide, phosphate back bone modifications to name a few (Dittmer et al Current Opinion in Microbiology vol. 6 Oct 2003 p. 472-477 under treatment of bacterial and parasitic infection with CpG containing oligonucleotides). Bacterial plasmid DNA induces an immune response in Salmonids (Jorgensen et al. Developmental and Comparative immunology 25 (2001) 313-32), however, the instant specification does not teach whether the instant nucleic acid molecules contain CpG motifs and if so whether they are effective in inducing a protective immune response against *P. salmonis*.

In view of the above considerations, the specification is not enabling for the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6-7, 9-16, 18-23, 25-27, 30-36 and 44-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because it is not clear whether the *P. salmonis* 45 kDa p45 protein is separate from the recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 – for example in claim 1, it can be interpreted that an isolated *P. salmonis* 45 kDa protein is being claimed separately (see recitation of *or*) from a recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution. Thus, any 45 kDa *P. salmonis* protein reads on claim 1. Clarification in the claims of the metes and bounds of what is being claimed is respectfully requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 46, 51, and 55 are rejected under 35 U.S.C. 102(b) as anticipated by Jones et al (Diseases of Aquatic Organisms vol. 33: 25-31, 1998).

Claim 1 and 46 is partially drawn to an isolated *P. salmonis* 45 kDa p45 protein. Claims 51 and 55 are partially drawn to an isolated *P. salmonis* 45 kDa protein wherein the protein has at least 95% identity with SEQ ID NO: 2 and/or SEQ ID NO: 4.

Jones et al teaches an isolated *P. salmonis* 45 kDa protein (p. 28 column 2 last bridging paragraph and p. 29 fig. 2). Said *P. salmonis* 45 kDa protein has at least 95% identity with SEQ ID NO: 2 and/or 4 absent evidence to the contrary.

Status of Claims

Claims 1,4,6,7,9-16,18-23,25-27,30-36 and 44-60 are rejected. Claims 7,9-16,20-23,25-27,30-36 and 44-54 are objected to. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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